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(54) Title: A METHOD OF ADMINISTERING LIPOSOMAL ENCAPSULATED TAXANE

(57) Abstract

Liposomal-encapsulated taxane or an antineoplastic derivative thereof or a mixture thereof is provided which is used to effect a therapeutically enhanced method of treating cancer. The liposomal encapsulated paclitaxel allows for administration to a patient, particularly a human patient, in less than one hour without substantial toxicity.

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A METHOD OF ADMINISTERING LIPOSOMAL ENCAPSULATED TAXANE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method of administering a liposomal encapsulated taxane.

BACKGROUND OF THE INVENTION

The use of taxanes, such as paclitaxel, as anti-tumor agents for patients suffering from diseases such as ovarian and breast cancer, is known. In addition, paclitaxel has been shown to be clinically potent as a synergistic agent when used in conjunction with radiation treatment. Paclitaxel has a unique mechanism of action and a broad spectrum of anticancer activity because paclitaxel shows stabilization of microtubules rather than disassembly of microtubules.

However, paclitaxel has extremely low solubility in water, which makes it difficult to provide a suitable dosage form. Currently, paclitaxel is prepared and administered in a vehicle containing Cremophor EL (a polyethoxylated castor oil) and ethanol in a 50:50 (vol/vol) ratio. This solution is diluted 1:10 in saline before being administered to humans. The stability of paclitaxel once diluted in saline solution is quite low. The drug degrades within 24 hours and, thus, handling of dosage for the patients becomes very difficult. Since, the drug precipitates from dilution, an on-line filter is utilized for the infusion of the drug to the patients.

In clinical trials, a consistent problem of anaphylactoid reaction, dyspnea, hypertension, and flushing have been encountered. The dose-limiting toxicity is myelosuppression which necessitates patient hospitalization when the drug is used.

Attempts to prevent paclitaxel cardiotoxicity and anaphylactoid reaction have included reliance on pretreatment of patients with antihistamine and corticosteroids, and by prolonging the infusion time from

six to twenty four hours. U.S. patent number 5,621,001 (Canetta et al.) discloses a prolonged infusion time in a method for reducing peripheral neurotoxicity symptoms while maintaining an anti-tumor effect in patients suffering from ovarian cancer and undergoing paclitaxel therapy. This method involves administering about 135 mg/m^2 of paclitaxel over a period of about 24 hours. The administration of paclitaxel is repeated at least once, about 21 days after the preceding administration.

U.S. patent number 5,665,761 (Canetta et al.) discloses a pretreatment stage before administration of paclitaxel. The '761 patent provides for paclitaxel infusions over a duration of less than six hours, preferably about three hours, utilizing dosages of between about 135 mg/m^2 and about 275 mg/m^2, preferably between about 135 mg/m^2 and about 175 mg/m^2, after patients had been pretreated to alleviate or minimize hypersensitivity responses. For example, the patients are pre-medicated with steroids, antihistamines, and H_2-antagonists sufficient to at least prevent an anaphylactoid shock capable of causing acute hypersensitivity reactions and patient death. U.S. patent number 5,670,537 (Canetta et al.) also discloses this method of administration for a patient suffering from a paclitaxel-sensitive tumor, such as an ovarian tumor.

U.S. Patent No. 5,641,803, discloses the administration of paclitaxel to a patient, wherein about 135-175 mg/m^2 of paclitaxel is administered over a period of about three hours. Such a period purportedly was used to overcome, in part, some of the aforementioned problems associated with short infusion times, such as one hour, which had been employed with the conventional paclitaxel formulations containing polyethoxylated castor oil.

In yet another attempt to address the toxicity concerns of the conventional paclitaxel formulation, U.S. Patent No. 5,696,153 suggests the use of an

administration regimen wherein 45 to 120 mg/m^2 of paclitaxel is administered over a period of 60 to 180 minutes, a plurality of times during a 21 day period, with each infusion being separated by an interval of between 4 to 5 days.

However, even with these manipulations of prolonged infusion time and pretreatment of patients with antihistamines and corticosteroids, the patients suffer from serious toxicities which are often fatal. Different agent delivery systems are being utilized to enhance tumor cell-fighting effects of the drug and/or reduce systemic toxicity. Liposomes are one of many carriers that have been developed to help anti-tumor agents become more efficient and less toxic. A "liposome" is a closed structure composed of lipid bi-layers surrounding an internal aqueous space.

U.S. patent number 5,648,090 (Rahman et al.)and U.S. Patent No. 5,424,073 (Rahman et al.) provide a liposomal encapsulated paclitaxel for a method for treating cancer in mammals using such a liposomal-encapsulated paclitaxel, or antineoplastic derivative thereof. The '090 and '073 patents disclose a method of modulating multidrug resistance in cancer cells in a mammalian host by administering to the host a pharmaceutical composition of a therapeutically effective number of liposomes which include a liposome-forming material, cardiolipin, and an agent such as paclitaxel, or an antineoplastic derivative of paclitaxel, or a mixture thereof; and a pharmaceutically acceptable excipient.

Up until the present invention the fastest administration time tolerated by most patients was optimally a three hour time period. Consequently, there is a need for methods for rapidly administering high concentrations of taxane in human cancer patients without inducing a toxic reaction. Such methods would improve the efficacy of taxane therapy and alleviate the discomfort and toxicity associated with previously known

taxane administration methods. The present invention provides such a method.

SUMMARY OF THE INVENTION

The present invention provides a method of administering relatively high concentrations of taxane to human patients over a short period of time. For example, taxane can be administered to humans in less than an hour in an amount from about 75 to 300 mg/m^2. Unique liposomal formulations of taxane or its antineoplastic derivatives facilitate such treatments. The method does not require premedication, as with anti-hypersensitivity agents, and is not accompanied by substantial toxic reactions in human patients. As a result, the present invention provides an improved method for treating cancer with taxane.

These and other advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

The invention may best be understood with reference to the following detailed description of the preferred embodiments.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method of administering a taxane to a patient, especially a human patient, in need of treatment with a taxane. In part, the present invention provides a delivery system for a taxane to a host which is characterized by the avoidance of solubility problems of a taxane; the improved taxane stability; the avoidance of anaphylactoid reactions and cardiotoxicity; the ability to administer a taxane as a bolus or short infusion, rather than an extended infusion of free taxane; the increased therapeutic efficacy of taxane; and the modulation of multidrug resistance in cancer cells.

The taxane is delivered in the form of a liposomal encapsulated taxane or antineoplastic derivative thereof. Any suitable taxane or derivative can be used in the present method. Suitable taxanes when used in accordance with the disclosed methods provide the aforementioned benefits. Preferably, the taxane is paclitaxel. A suitable derivative of paclitaxel is taxasm. Other suitable taxanes are 7-epipaclitaxel, t-acetyl paclitaxel, 10-desacetyl-paclitaxel, 10-desacetyl-7-epipaclitaxel, 7-xylosylpaclitaxel, 10-desacetyl-7-glutarylpaclitaxel, 7-N,N-dimethylglycylpaclitaxel, 7-L-alanylpaclitaxel, taxotere, and mixtures thereof.

The pharmaceutical composition may also include a suitable cardiolipin. Suitable cardiolipin may be from either a natural or synthetic source. The taxane, such as paclitaxel, is encapsulated in liposomes using the cardiolipin. In addition to cardiolipin, the taxane may be encapsulated in liposomes with phosphatidylcholine and cholesterol. Such lipid compositions provide over 90% encapsulation of the drug in liposomes.

The liposomal encapsulated taxane can be prepared by any suitable process. For example, the taxane or a derivative thereof can be dissolved in a suitable solvent. Generally, suitable solvents are non-polar or slightly polar and can be evaporated without leaving toxic residue behind. Suitable solvents include such diverse solvents as ethanol, methanol, chloroform, butanol or acetone. Cardiolipin can also be dissolved in a suitable solvent as described for taxane and the taxane and the cardiolipin solutions can be mixed. The remaining lipophilic material can be dissolved in a suitable solvent, which may be the same as or different from the taxane containing solvent. The solvent will have low polarity such as chloroform, butanol or a non-polar solvent, such as n-hexane. The solvent mixture containing the taxane and cardiolipin can be mixed with

the solution containing the remaining lipophilic components.

The solvent is removed, from the mixture by a suitable method such as by lyophilization to afford a dry lipid film that contains the drug. The mixture is stored in this form, optionally under an inert gas atmosphere, such as an N_2 atmosphere. The dry lipid film can be stored at low temperatures, such as -20° C for extended periods of time until liposomes are hydrated and prior to use.

Liposomes can be formed by adding any suitable solution to the lipid film. Typically, suitable solutions are polar solutions, preferably, aqueous saline solutions. Once the solution is added, liposomes can be formed by mixing, for example, as by vortexing. Where smaller vesicles, such as unilamellar vesicles, are desirable the solution can be sonicated. In certain methods, suitable preparations can be mixtures of multilamellar vesicles and unilamellar vesicles.

The liposome is a closed structure composed of lipid bilayers surrounding an internal aqueous space. Generally, the liposomes may be neutral, negative or positively charged liposomes. For example, positively charged liposomes can be formed from a solution containing phosphatidyl choline, cholesterol, and stearyl amine. Negative liposomes can be formed, for example, from solutions containing phosphatidyl choline, cholesterol, and phosphatidyl serine or more preferably, cardiolipin. Other additives can also be included in the liposomes to modify the properties of the resulting preparations. For example, preferred preparations also include α-tocopherol.

Storage conditions can vary. Preferably, mixtures of lipophilic components are stored as dry lipid films at about -20° C. Once hydrated, liposome suspensions of the pharmaceutical composition can be stored and are stable in buffered, neutral pH saline solutions for periods of

hours to months, depending upon the temperature, paclitaxel content, and phospholipid constituents.

The liposomal drug delivery system which features a high drug to carrier ratio can alter drug pharmacokinetics, maintaining the plasma concentration of the drug at an increased level over a longer period of time. The biodegradability and the low inherent toxicity and immunogenicity of liposomal preparations reduces toxicity with respect to free-floating taxanes in the plasma.

The present liposomal formulations provide a drug-delivery system which allows infusion of high concentrations of taxane in a relatively stable form and which provides sustained therapeutic benefits at target sites, while maintaining low concentrations of insoluble free taxane and minimal adverse toxic effects than were previously known. For example, infusion of encapsulated paclitaxel provides higher peak plasma concentrations, longer presence of the drug in the body, and higher AUC ("area under the curve" measurement of plasma concentration over time) than the conventional paclitaxel.

The present pharmaceutical composition can be administered in amounts of at least 50 to 300 mg of active compound/m^2 of mammalian host surface area, within a period of less than about three hours, preferably in less than about one hour, and most preferably 45 minutes without causing a substantial toxic reaction. For example, in a 70 kg human, about 0.5 to 5.0 mg active compound per kg of body weight can be safely administered in about 45 minutes. Preferably, about 1.0-3.0 mg of active compound per kg of body weight is administered. Alternatively, preferable amounts include 75, 135, 175, 250, and 300 mg/m^2.

Liposomal encapsulated taxane has a substantial beneficial effect in overcoming multidrug resistance in cancer cells which are subjected to chemotherapy. By

using the liposomal composition of the present invention, it is possible to reduce the tendency of cancer cells subjected to chemotherapy to develop resistance to the chemotherapeutic agents used for chemotherapy such as anthracycline glycosides. This method includes administering to a host a pharmaceutical composition of a liposomal encapsulated taxane of the present invention in accordance with the administration protocol.

Taxanes and the anti-neoplastic derivatives thereof may be used to treat any form of mammalian cancer. Such compounds are thought to function by promoting the assembly of microtubules or prohibiting the tubulin disassembly process. Taxane and the anti-neoplastic derivatives thereof are of particular advantageous use in the treatment of mammalian lymphoma, ovarian, breast, lung and colon cancer, and particularly those conditions in humans.

The present liposome compositions can be administered intravenously, intraperitoneally, to an isolated portion of a mammalian body particularly a human body, such as an arm or leg, or in the case of a human, a hand, or can be injected directly into a tumor.

The following examples further illustrate the present invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

Paclitaxel can be encapsulated in liposomes of cardiolipin, phosphatidylcholine, cholesterol and α-tocopherol. The composition described in this example, provides for over 90% encapsulation of the drug in liposomes. The paclitaxel in liposomal formulation is stable for days at room temperature and at -20° C for at least 5 months. No degradation or precipitation of paclitaxel is observed at any storage temperature and the preparation appears to be ideally suited for systemic administration in accordance with the present invention.

The proportion of lipids per mg of paclitaxel is:

1.8 mg cardiolipin
9.0 mg phophatidylcholine
3.0 mg cholesterol
0.1 mg ∝-tocopheryl

The liposome encapsulated paclitaxel can be manufactured using the following procedure.

8.89 kilograms of t-butyl alcohol are added to a 12.0 liter flask and heated to 40-45° C. The following additions are made sequentially with mixing until dissolution and heating at 40-45° C: 3.412 grams of D-α-tocopheryl acid succinate, 205 grams of egg phosphatidylcholine, 22.78 grams of paclitaxel, 41.00 grams of tetramyristoyl cardiolipin, 68.33 grams of cholesterol.

The resulting solution is filtered through a 0.22 micron filter. The resulting filtrate is filled into sterile vials, each containing about 10.1 grams of filtrate. The vials are stoppered and subjected to lyophilization. They can be stored at -20° C until use.

Liposomes are prepared from the dry lipid film, as needed, with 25 ml of normal saline solution. The mixture is allowed to hydrate at room temperature for about one hour, after which time the vials are vortexed for about one minute and sonicated for about 10 minutes in a bath type sonicator at maximum frequency. An appropriate amount of the contents of the vial can be transferred to an infusion bag and infused into a patient in accordance with the present invention.

EXAMPLE 2

The following study demonstrates that a large quantity of taxane can be rapidly administered to humans without inducing a substantial toxic reaction. Both hematological toxicity and nonhematological toxicity were evaluated. In addition, the study was used to determine in human patients the dose-limiting toxicity, the maximum

tolerated dose and the untolerated dose for the liposomal formulation described in Example 1.

Vials containing liposomal paclitaxel were prepared as in Example 1. The preparations were 1 mg/ml paclitaxel in liposomes. The contents of the vials were transferred to infusion bags at the appropriate dosages and administered to patients over about a 45 minute period.

Patients selected for the study had a measurable or evaluable metastatic or locally recurrent malignancy and had no significant hope of cure or palliation by other conventional therapies. In addition, they had no evidence of spinal cord compression or carcinomatous meningitis. Patients had not undergone chemotherapy or radiotherapy within the four weeks prior to treatment. Those patients that had undergone prior chemotherapy or radiotherapy exhibited complete hematologic recovery prior to treatment in this study. All patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1 and had a life expectancy of at least 3 months. Patients in the study were all over the age of 18, were free of infection and had recovered from the effects of any major surgery which must have occurred more than three weeks prior to entering the study. Within the immediate two weeks prior to the instant tests all patients had a white blood cell count of over $3000/mm^3$, a platelet count of over $100,000/mm^3$, serum creatinine of less than 1.8 mg/dl or creatinine clearance of more than 60/cc/min and serum bilirubin of less than 1.5 mg/dl.

Treatments were administered intravenously over about a 45 minute period. At least three patients were treated at each dosage level. Dosages were about 90 mg/m^2, 135 mg/m^2, 175 mg/m^2, 250 mg/m^2, and 300 mg/m^2 allowing for normal laboratory and therapeutic dose variation. The formulation was given as a single agent without pretreatment with steroids, antihistamines or

other therapeutic agents such as anaphylaxis inhibitors. Where the treating physician considered it appropriate, treatments were repeated every 21 days. Each patient was subjected to a single treatment regimen.

Hematologic toxicity was evaluated in test patients by taking blood specimens of 5 mls from each patient. Samples were taken just prior to drug infusion, at the end of the infusion (time=0), then at 2, 4, 6, 10, 20, 30, 60, 240 minutes and 24 hours after infusion. The samples were collected in heparinized tubes which were gently inverted after filling to ensure mixing of the heparinized blood. The vials were kept cool until the plasma was isolated from each sample. As soon as practical, the samples were centrifuged at 2000 rpm, for 15 minutes to collect the plasma layer. Approximately 1 or 2 ml of the plasma was transferred to a cryotube which was capped and immediately frozen at -20° C in an upright position until hematological toxicity analysis. Nonhematological toxicity and drug efficacy were also evaluated. The results of this study are shown in Table I below.

Common toxicity grades established by the National Cancer Institute were employed to determine drug toxicity. Dose-limiting toxicity is defined as any grade 3 or higher non-hematologic toxicity for 7 or more days occurring during cycle 1 of chemotherapy. An untolerable dose is defined as the dose level at which at least 1/3 to 2/3 of the patients have dose-limiting toxicity. The maximum tolerated dose level is defined as the dose level at which 0/6 or 1/6 patients experience dose-limiting toxicity and at least 2/3 or 4/6 patients treated at the next higher dose level experience dose-limiting toxicity.

This study demonstrated that a large quantity of taxane could be administered to a human without inducing a substantial hematological or nonhematological toxic reaction. Nonhematological toxicity was generally minor but became more pronounced at the highest dosage level.

Similarly, hematological toxicity was mild but became more pronounced at the highest dosage. At least 300 mg/m^2 of taxane could be administered to a human patient in a 45 minute period without inducing substantial hematological toxicity or anaphylaxis. The dose limiting toxicity was about 300 mg/m^2 when drug was administered in a 45 minute period. The untolerable and maximum tolerable doses were not determinable from this study but were at least 300 mg/m^2. With one exception, the cancer had not progressed or was improved in each of the patients studied.

TABLE I

Patient Number	Treatment Cycles	Dose (mg/m^2)	Heme Toxicity[1]	Nonhematological Toxicity	Best Response	Off study due to
001	2	90	None	HSR[2]		P.D.[3]
002	11+	90	Mild		Stable	
003	6	90	Mild	(Seizure)	Stable	P.D.
004	2	135		HSR		P.D.
005	6	135	Mild	Muscular & hepatic	Stable	elective
006	8+	135	Mild	(HA, fever, pharyngitis, wheezing)	Progressed	
007	3	175	Mild	(diarrhea)		P.D.
008	2	175	Mild	Mild hepatic		P.D.
009	1	175	Mild	Recurrent HSR; Nausea/fatigue; Mild hepatic		HSR
010	2	250	Mod	(hemoptysis)		P.D.
011	4+	250	Mild	Mild hepatic (HA, diarrhea, chills & sweats) Esophagitis grade3 after cycle 3	Stable	
012	3	250	Mild	Mild hepatic		P.D.
013	2+	250	Mild	Mild GI, HSR		
014	2+	300	Mod	Hepatic, Esophagitis grade 3	Improved	
015	1+	300	Severe	Mild HSR, Hepatic		
016	1+	300	Severe	Esophagitis grade 3		

[1] neutropenia, anemia, thrombopenia
[2] hypersensitivity reaction: flushing, back pain, pruritis
[3] physician or patient discretion

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WE CLAIM:

1. A method of administering taxane to a patient in need of treatment with taxane comprising administering a pharmaceutical composition over a period of less than an hour in an amount from about 75 to 300 mg/m^2 wherein said pharmaceutical composition is liposomal encapsulated taxane or an antineoplastic derivative thereof.

2. The method of claim 1 wherein said taxane is selected from the group consisting of paclitaxel, 7-epipaclitaxel, t-acetyl paclitaxel, 10-desacetyl-paclitaxel, 10-desacetyl-7-epipaclitaxel, 7-xylosylpaclitaxel, 10-desacetyl-7-glutarylpaclitaxel, 7-N,N-dimethylglycylpaclitaxel, 7-L-alanylpaclitaxel, taxotere, and mixtures thereof.

3. The method of claim 1 wherein said pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

4. The method of claim 1 wherein said pharmaceutical composition further comprises cardiolipin.

5. The method of claim 4 wherein said cardiolipin is selected from the group consisting of natural cardiolipin and synthetic cardiolipin.

6. The method of claim 1 wherein said amount of said taxane is about 75 mg/m^2.

7. The method of claim 1 wherein said amount of said taxane is about 135 mg/m^2.

8. The method of claim 1 wherein said amount of said taxane is about 175 mg/m^2.

9. The method of claim 1 wherein said amount of said taxane is about 250 mg/m^2.

10. The method of claim 1 wherein said amount of said taxane is about 300 mg/m^2.

11. The method of claim 1 wherein said patient is suffering from a ovarian cancer, breast cancer, lung cancer or other neoplasm.

12. The method of claim 1 wherein said liposomal encapsulated taxane is administered by intravenous infusion.

13. The method of claim 12 wherein said liposomal encapsulated taxane is administered over a period of 45 minutes.

14. The method of claim 12 wherein said administration of said liposomal encapsulated taxane is repeated at least once every 21 days.

15. The method of claim 1 wherein said administration of said liposome encapsulated taxane administered intraperitoneally to patients suffering from cancer.

16. The method of claim 15 wherein said administration of said liposome encapsulated taxane is administered intraperitoneally to patients suffering from colon cancer.

17. A method of treating a human with taxane comprising administering rapidly a large quantity of liposomal taxane to a human without inducing a substantial toxic reaction.

18. The method of claim 17 in which the liposomal taxane is administered intravenously.

19. The method of claim 17 in which the liposomal taxane is administered as a single agent without pretreatment by steroids, antihistamines or other therapeutic agents.

20. The method of claim 17 in which substantial nonhematological toxicity is not induced.

21. The method of claim 17 in which substantial anaphylaxis is not induced.

22. The method of claim 17 in which the large quantity of liposomal taxane ranges from about 75 to 300 mg/m^2.

23. The method of claim 17 in which the large quantity of liposomal taxane ranges from about 90 to 300 mg/m^2.

24. The method of claim 17 in which the large quantity of liposomal taxane ranges from about 135 to 300 mg/m^2.

25. The method of claim 17 in which the large quantity of liposomal taxane ranges from about 175 to 300 mg/m^2.

26. The method of claim 17 in which the large quantity of liposomal taxane ranges from about 175 to 250 mg/m^2.

27. The method of claim 17 in which the large quantity of liposomal taxane is about 250 mg/m^2.

28. The method of claim 17 in which the liposomal taxane is rapidly administered in less than 3 hours.

29. The method of claim 17 in which the liposomal taxane is rapidly administered in less than 1 hour.

30. The method of claim 17 in which the liposomal taxane is rapidly administered in about 45 minutes.

31. The method of claim 17 further comprising repeating the step of administering rapidly a large quantity of liposomal taxane to a human without inducing substantial hematological or nonhematological toxicity.

32. The method of claim 31 wherein the repeating step occurs in 21 days.

33. A method of treating a human with taxane comprising intravenously administering to a human in about 45 minutes about 175 to 300 mg/m^2 of a liposomal taxane formulation that has a dose limiting toxicity of

at least about 300 mg/m^2 when administered in about 45 minutes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14986

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 9/127
US CL :424/450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS:
Search terms: taxane, taxol, ?paclitaxel, liposome?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,424,073 A (RAHMAN et al) 13 June 1995, abstract, Examples and column 8, lines 28-52.	1-9, 11-12 & 15-26 ---------------- 10, 13-14 & 27-33
Y	US 5,756,537 A (GILL) 26 May 1998, abstract, Figures, column 2, lines 23 through column 3, line 2, column 6, lines 45-67, examples and claims.	1-33
Y	US 5,683,715 A (BONI et al) 04 November 1997, abstract, examples and claims.	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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